Movement Disorders
CLINICAL PRACTICE

CASE REPORT

Treatment of Isolated Dystonia with Zolpidem

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Isolated dystonia is a rare movement disorder characterized by involuntary, repetitive, sustained muscle contractions or postures of the entire body, occasionally resulting from actions of the DYT1 gene or DYT6 gene. There are several treatment options, including pharmacological therapies such as the use of anticholinergics (most commonly trihexiphenydil) and surgical approaches such as DBS of the internal globus pallidus (GPi-DBS). However, these treatments are notoriously difficult and often unsuccessful. Zolpidem, an imidazopyridine agonist with a high affinity for the benzodiazepine subtype receptor ω1, has been reported to improve the symptoms of Parkinson's disease.[1] Recently, several reports have also demonstrated the beneficial effect of zolpidem in treating various types of dystonia, including those caused by basal ganglia dysfunction.[2] Here, we report on 2 patients with isolated dystonia who were successfully treated with zolpidem.

Patient 1 was a 35-year-old man with a 15-year history of generalized torsion dystonia carrying the DYT6 mutation, whose case has been previously reported on.[3] At the age of 30, he underwent GPi-DBS, which improved his symptoms (Burke-Fahn-Marsden Dystonia Rating Scale-Motor score [BFMDRS] was reduced from 55 to 21). However, a few years later, his symptoms worsened (BFMDRS was 58). He had been receiving trihexyphenidyl (≤12 mg/day) and clonazepam (1–3 mg/day) with no benefits. At the age of 35, we treated him with zolpidem (10 or 20 mg a time), and his symptoms significantly improved in a dose-dependent manner (10 mg, BFMDRS 33.5; 20 mg, BFMDRS 25.5; Fig. 1). He received 10 or 20 mg of zolpidem, and its beneficial effect was noted within 30 minutes; its duration of action was approximately 4 hours. Two years later, he was still receiving zolpidem 10 mg in the morning and evening with continued beneficial effects (BFMDRS score reduced from 58 to 35).

Patient 2 was a 20-year-old man with a 6-year history of generalized torsion dystonia. He had no brain lesion in the basal ganglia, as detected by 1.5 T MRI and no history of antipsychotic drug administration and traumatic injury. Genetic testing demonstrated no mutation in the currently known DYT genes.

At the age of 18, he underwent GPi-DBS, which improved his symptoms (BFMDRS was reduced from 71.5 to 22.5). However, at the age of 20, his DBS device was removed because of a skin infection and his symptoms worsened again (BFMDRS 57). He was tried on medication with trihexiphenidyl (≤12 mg/day) and baclofen (≤30 mg/day), with no effect. We suggested that the patient should be started on zolpidem (10 or 20 mg at once), and his symptoms significantly improved in a dose-dependent manner (10 mg, BFMDRS 27; 20 mg, BFMDRS 19). Improvement was noticed within 20 to 30 minutes of dose administration and was optimal 2 hours later. The response to each dose lasted for 4 hours. Six months later, he was still receiving zolpidem 10 mg in the morning and evening with continued beneficial effects (BFMDRS score reduced from 64.5 to 27).

In this study, 2 patients with isolated dystonia, 1 of whom had DYT6, significantly responded to zolpidem. The most beneficial results, using pallidal DBS, were reported in children with primary generalized dystonia, otherwise known as DYT1 dystonia. However, it was reported that DYT6 patients appear to respond less well to GPi-DBS than DYT1 patients.[4] In our present case study, the DYT6 patient showed a moderate improvement from GPi-DBS, yet these beneficial effects gradually diminished after a few years. This suggests that zolpidem may be a useful option for treating patients with generalized torsion dystonia who have previously responded poorly to GPi-DBS, regardless of their genetic profile. It may likewise be useful regardless of whether the patients have undergone DBS surgery before.

Infection is a serious complication of DBS implantation and commonly requires device removal for cure. In our present case study, patient 2 presented with head skin infection after 1 year

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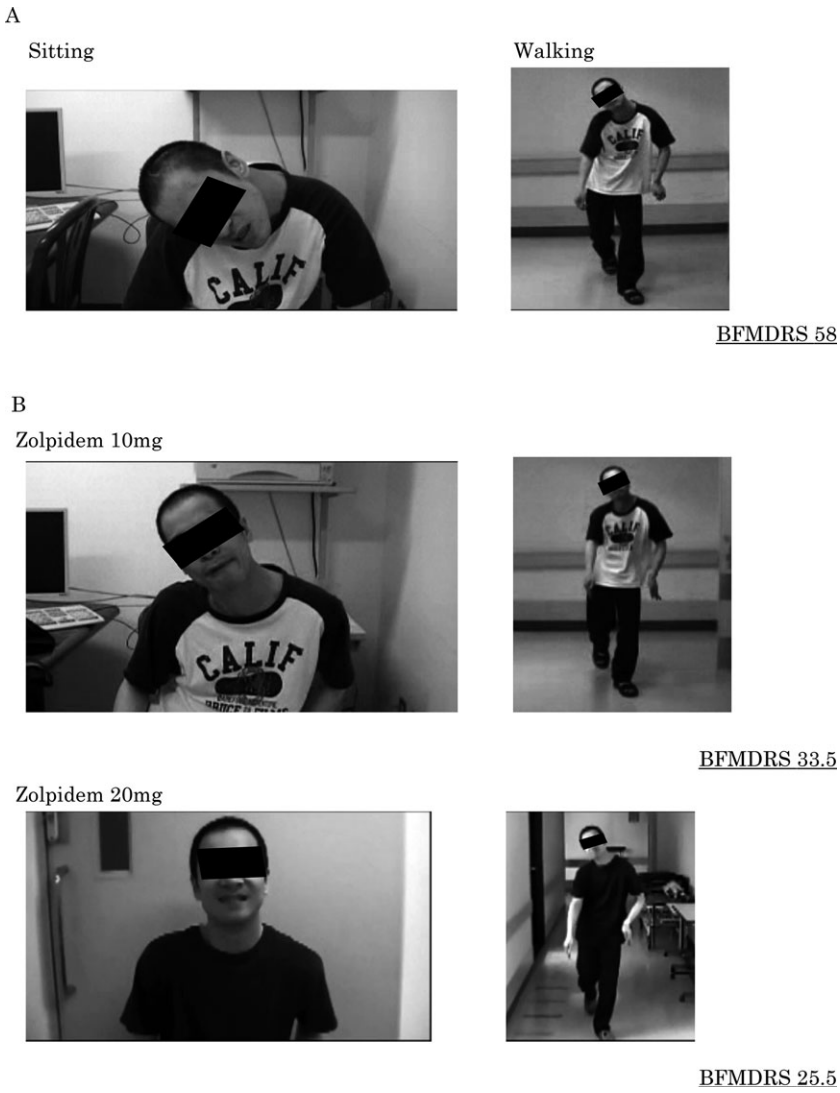

Figure 1 Zolpidem thrapy for DYT6 dystonia patient (patient 1); 5 years after GPi-DBS operation. (A) It is before treatment. The score of BFMDRS was 58. (B) Three hours after oral zolpidem (10/20 mg) administration. His cervical dystonic symptoms improved, the score of BFMDRS was decreased from 58 to 33.5 (10 mg) and to 25.5 (20 mg). His symptoms significantly improved dose dependently.

postoperatively. Finally, DBS infection was cured with prolonged antibacterial treatment associated with total hardware removal, but his dystonic symptoms worsened and a new DBS system could not be implanted within at least 6 months after DBS infection. His symptoms significantly improved by zolpidem and continued beneficial effects for 6 months; we consider that zolpidem may be a useful treatment option for patients such as this who could not be implanted with a DBS system because of infection.

Adverse effects, such as severe drowsiness, was the dose-limiting factor. In this study, 2 patients used zolpiedem doses up to 20 mg once in the morning, but moderate-to-severe drowsiness occurred. They used zolpidem 10 mg immediately twice a day; their beneficial effects were continued without severe drowsiness.

Zolpidem is an imidazopyridine agonist with a high affinity for the benzodiazepine site of GABAA receptors containing $\alpha 1$ subunit in combination with $\beta 2$ and $\gamma 2$ subunits present in interneurones in all brain areas, including the hippocampus, thalamus,[5] STN,[6] cortex, and cerebellar Purkinje cells.[7] After binding to these sites, zolpidem might enhance inhibitory pathways in the basal ganglia motor loop, which may, in turn, account for the clinical improvement in dystonia.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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Disclosures

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Supporting Information

Videos accompanying this article are available in the supporting information here.

Video 1. Case 1. Before treatment.

Video 2. Case 1. Three hours after oral zolpidem (20 mg) administration. His symptoms significantly improved dose dependently.

Video 3. Case 2. Before treatment.

Video 4. Case 2. Three hours after oral zolpidem (20 mg) administration. His symptoms significantly improved dose dependently.

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